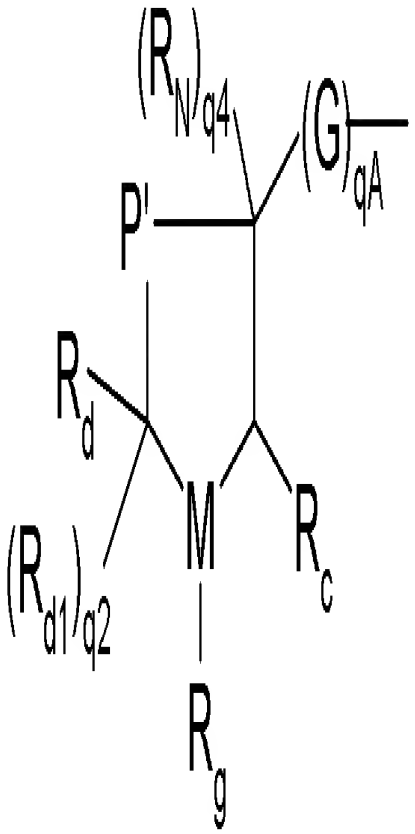

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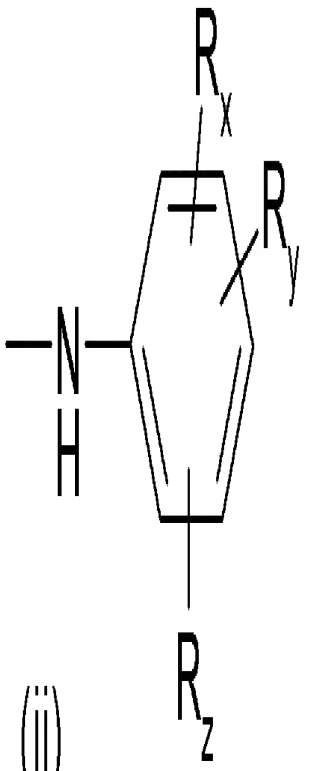

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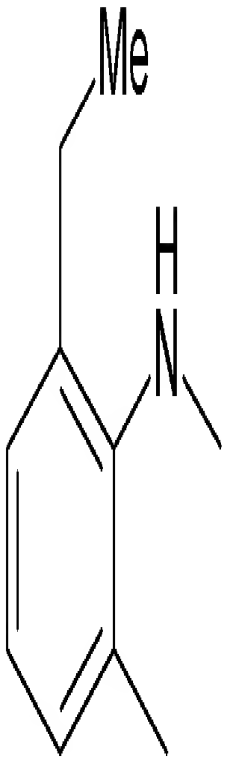

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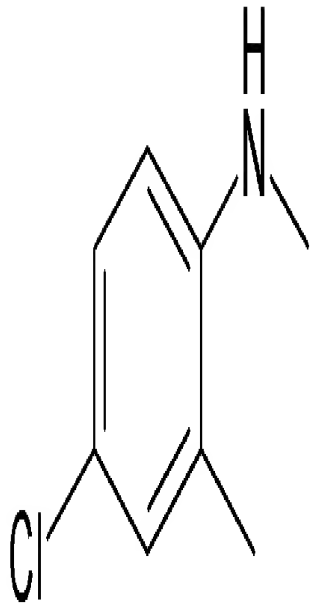

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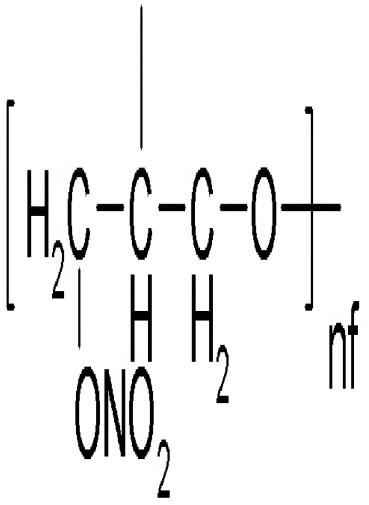

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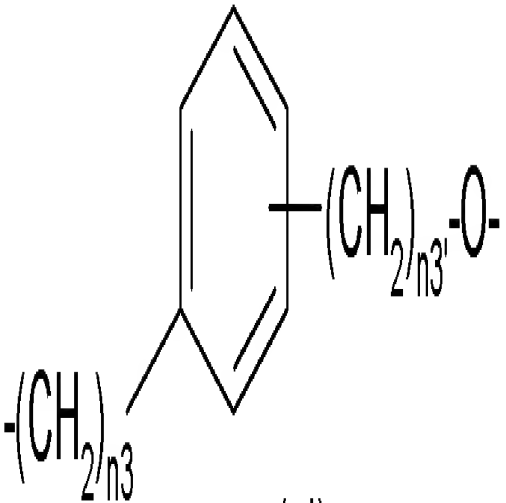

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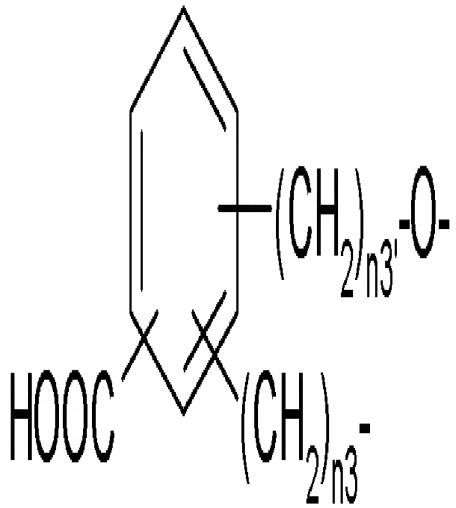

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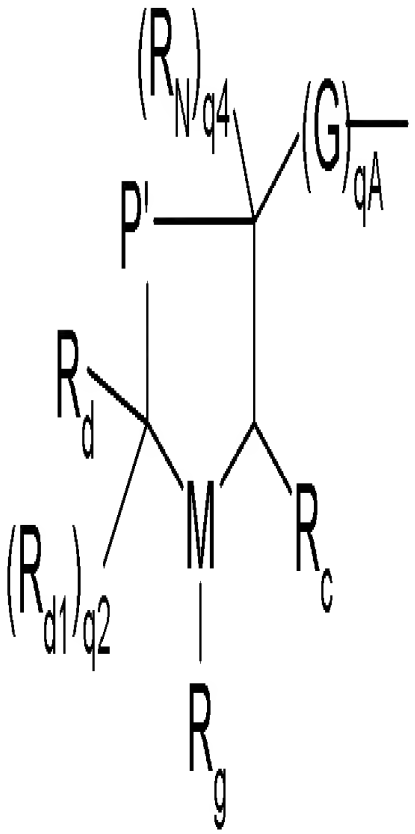

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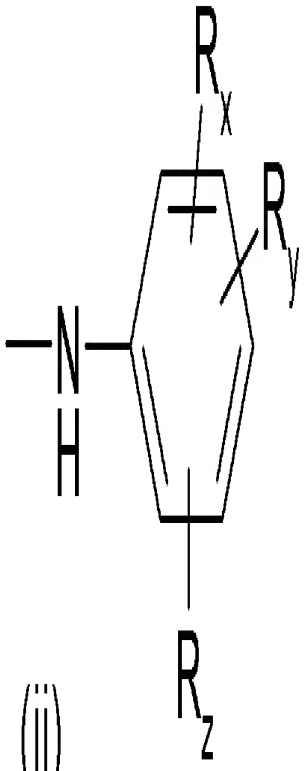

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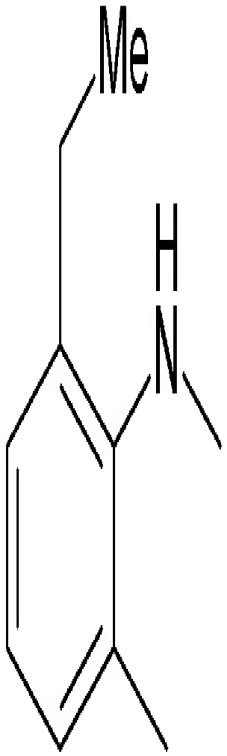

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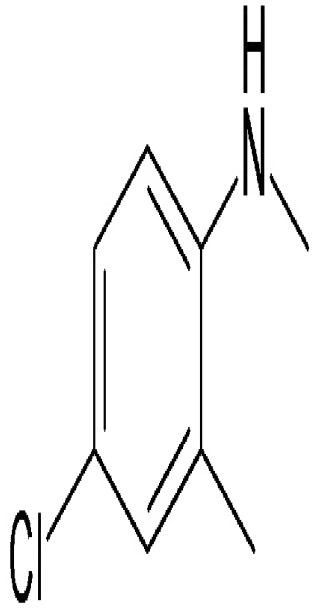

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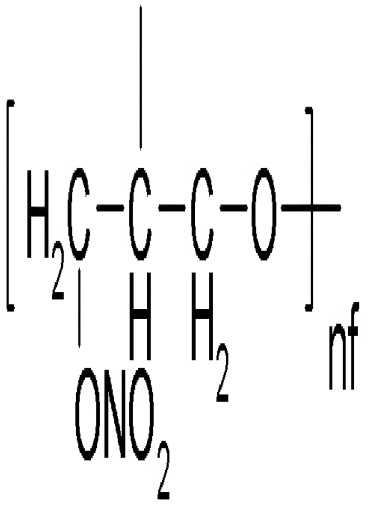

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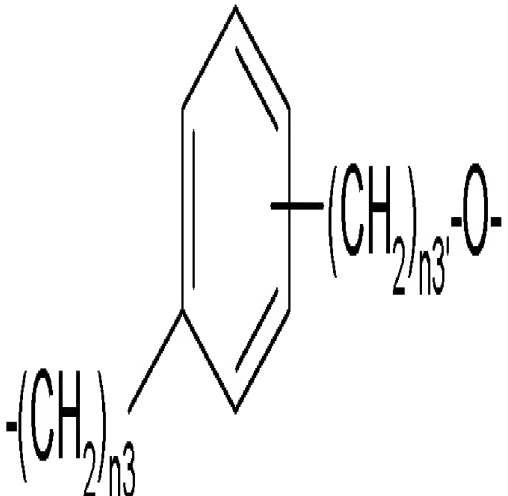

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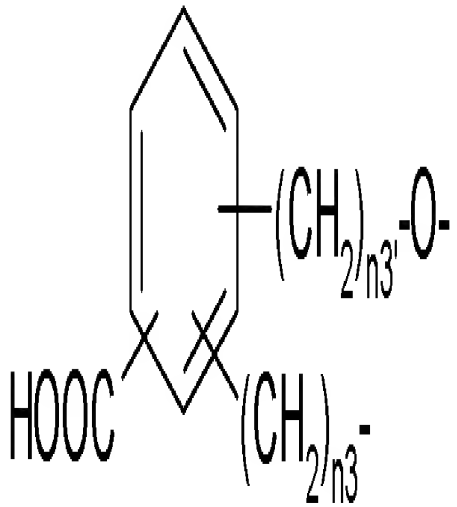

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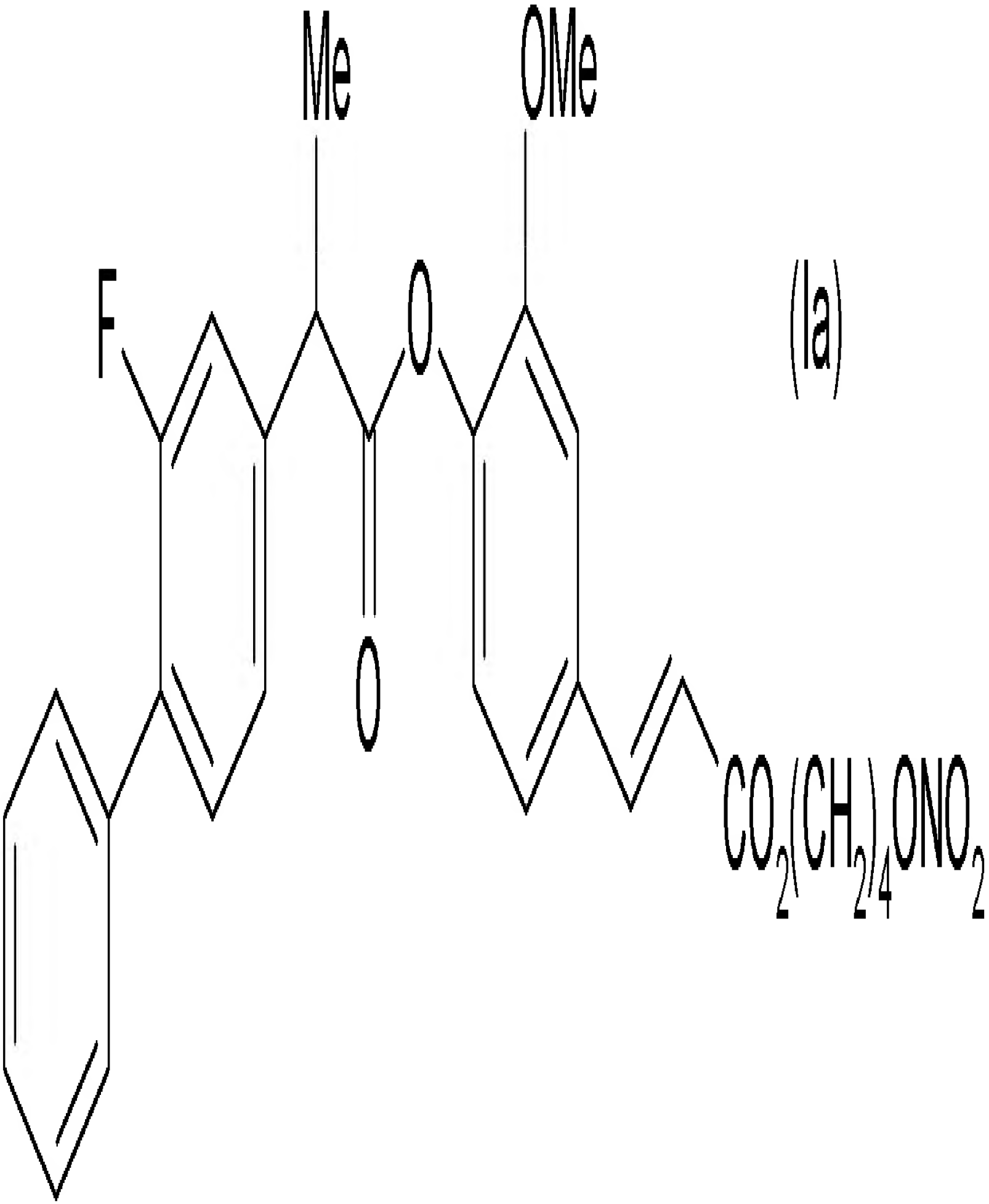

(Ia)

DERWENT-ACC-NO: 2003-112030

DERWENT-WEEK: 200611

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TITLE: Use of nitrooxy derivatives for treating e.g. Alzheimer disease

INVENTOR: DEL SOLDATO P

PATENT-ASSIGNEE: NICOX SA[NICON]

PRIORITY-DATA: 2001IT-MI0985 (May 15, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE
WO 02092072 A2	November 21, 2002	EN
AU 2002312897 A1	November 25, 2002	EN
IT 1324845 B	December 2, 2004	IT
AU 2002312897 A8	October 13, 2005	EN

DESIGNATED-STATES: AE AG AL AU BA BB BG BR BZ CA CN CR CU CZ DM DZ EE GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX NO NZ PL RO SG SI SK TR TT UA US UZ VN YU ZA AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE L S LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
WO2002092072A2	N/A	2002WO-EP05165	May 10, 2002
IT 1324845B	N/A	2001IT-MI0985	May 15, 2001
AU2002312897A1	N/A	2002AU-312897	May 10, 2002
AU2002312897A8	Based on	2002AU-312897	May 10, 2002

INT-CL-CURRENT:

TYPE	IPC DATE
CIPS	A61K31/215 20060101
CIPS	A61K31/24 20060101
CIPS	A61K31/404 20060101
CIPS	A61K31/44 20060101
CIPS	A61P25/28 20060101

ABSTRACTED-PUB-NO: WO 02092072 A2

BASIC-ABSTRACT:

NOVELTY - Nitrooxy derivatives (I) are used in the preparation of a drug for the prophylaxis and treatment of Alzheimer disease.

DESCRIPTION - Nitrooxy derivatives of formula A-(B)ba-(C')ca-NO2 (I) or their salts are used in the preparation of a drug for the prophylaxis and treatment of Alzheimer disease.

ba, ca = 0 or 1;

A = R-T1;

R = a group of formula (i);

G = CH=CH or C((Ra)(Rb));

M = C or N;

P' = C((Re)(Re1)q3)-(Q)q1;

Q = CH or O;

qA, q1-q4 = 0 or 1;

Rc = H, 1-3C alkyl or a group of formula (ii);

Rx, Ry, Rz = H, halo, 1-3C alkyl or CF3;

Rg = H or OCH3 when (i) has a 5-membered ring or an electronic doublet when the 6-membered ring is aromatic and M is N, or p-chlorobenzoyl when q1 is 0 and M is N and (i) is aromatic, or

Rc + Rg = a group of formula (iii);

Rd = H, OH, 1-4C alkyl optionally branched, phenyl or 2-oxo-cyclopentylmethyl;

Re = H, halo or benzoyl, or

Rd + Re = CH=CH-C(OMe)=CH or a group of formula (iv);

Rd1 = H when q2 is 1;

Re1 = H when q3 is 1;

RN = 1-3C alkyl;

T1 = (CO)t or (X)t';

X = O, S or NR1c;

R1c = H or 1-5C alkyl;

t, t' = 0 or 1;

B = Tb-X2-Tbi;

Tb = CO when the reactive function in the precursor is OH or NH2 or X when the reactive function in the precursor is COOH;

Tbi = (CO)tx or (X)txx;

tx, txx = 0 or 1;

X2 = a bivalent linking group;

C' = Tc-Y;

Y = m1, m2 or m3;

m1 = (C)n1((Rk1)(Rk2))-Y3-(C)n2((Rk3)(Rk4))-O;

n1 = 0-3;

n2 = 1-3;

Rk1-Rk4 = H or 1-4C alkyl;

Y3 = 5- or 6-membered heterocyclyl containing 1 or 2 N atoms;

m2 = R'O, (CH2-CH(ONO2)-CH2-O)nf', group of formula (v), (CH(R1f)-CH2-O)nf or (CH2-CH(R1f)-O)nf);

R' = 1-20C alkyl or 5-7C cycloalkylene;

nf' = 1-6;

R1f = H or CH3;

nf = 1-6;

m3 = a group of formula (vi) or (vii);

n3 = 0-3;

n3' = 1-3;

X2 = bivalent group, such that in Tb-X2-Tbi (which is the corresponding precursor of B), the free valences of Tb and Tbi are saturated with OZ, Z or -N(Z1)(Z2), and

Z, Z1, Z2 = H or 1-10C alkyl,

provided that:

(1) ca and ba are not both zero;

(2) The carbon atom of P' is on position 5 of the ring of R;

(3) when the ring in (i) is aromatic and Q is CH, then q2-q4 are 0, and when the ring in (i) is a 6 membered saturated ring and Q is O in position 6 of the ring, then q2-q4 is 1;

(4) when qm is 1 and G is -C((Ra)(Rb))-, then Ra and Rb are H or 1-3C alkyl;

(5) when q2 is 1, then Rd1 is H;

(6) when q3 is 1, then Re1 is H;

(7) when q4 is 1, then Rn is 1-3C alkyl;

(8) when t' is 0, then t is 1, and when t' is 1 then t is 0;

(9) when txx is 0, then tx is 1 and when txx is 1 then tx is 0;

(10) when ba and ca are 1, then Tc is CO;

(11) when tx is 0, then Tc is X;

(12) when txx is 0, then X is O, S or NR1c;

(13) when ba is 0, Tc is C(O);

(14) when t is 0, then Tc is X;

(15) when t' is 0, then X is O, S or NR1c;

(16) when ba is 0, Y is R'O, then R is ferulic acid or flurbiprofen;

(17) Z1 and Z2 are Z, when Tb and/or Tbi is CO or X, in function of values t, t', tx and txx, and

(18) for the cycloalkylene ring in m2, at least one carbon atom is optionally substituted by a heteroatom having side chains of R' type.

(I) Satisfies the following test (test 4): analytical determination carried out by adding aliquots of methanolic solutions at 10 power -4 M concentration of the precursor of B to a methanolic solution of DPPH (2,2-diphenyl-1-picrylhydrazyl); after having maintained the solution at room temperature and sheltered from light for 30 minutes, the absorbance of the test solution and of a solution containing only DPPH in the same amount is read, at a wavelength of 517 nm; then the inhibition percentage of the precursor of B towards the radical production induced by DPPH is determined by the formula: (1-As/Ac)x100, where As and Ac are respectively the absorbance values of the solution containing the test compound and DPPH and that of the solution containing only DPPH. The acceptance criterion of the precursor compounds of B according to this test is the following; test 4 is satisfied by the precursor compounds of B when the inhibition percentage as above defined is at least 50%.

Amyloid plague deposit inhibitor.

In a test, 72 male rats (3 months old) divided in 5 groups were chronically infused with lipopolysaccharide (LPS) for 30 days and received once a day for the same period, by subcutaneous injection respectively NO-ASA (302 micro-moles/kg), NO-flurbiprofen (14 micro-moles/kg), NO-C4-flurbiprofen (41.5 micro-moles/kg), flurbiprofen (12.3 micro-moles/kg) or the same volume of solvent (controls). Results showed that the nitrooxy

derivatives, NO-flurbiprofen and NO-C4-flurbiprofen were more effective in inhibiting the neurodegenerative process induced by LPS with respect to NO-ASA. NO-flurbiprofen showed 45% inhibition.

USE - Used in the prophylaxis and treatment of the Alzheimer disease.

ADVANTAGE - (I) Prevent the deposition of amyloid plague, with a higher efficacy than that of the products of the prior art. (I) Have good tolerability after a long treatment, so that (I) can be used in very advanced pathology conditions.

EQUIVALENT-ABSTRACTS:

ORGANIC CHEMISTRY

Preferred Compound: The precursor compound of B is an amino acid (preferably L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione or their esters (preferably ethyl or isopropyl ester), hydroxyacid (preferably gallic acid, ferulic acid, gentisic acid, citric acid, caffeic acid, dihydrocaffeic acid, para-cumaric acid or vanillic acid), aromatic and heterocyclic polyalcohol (preferably nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulphuretin, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductive acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, para-cumaric alcohol, 4-hydroxy-phenylethylalcohol, coniferyl alcohol or allopurinol) or compounds containing at least one free acid function (preferably 3,3'-thiodipropionic acid, fumaric

acid, dihydroxymaleic acid or edetic acid). Preferred Compounds: If (I) has at least one chiral centre, then (I) is used in racemic form, as a mixture of diastereoisomers, or as a single enantiomer or diastereoisomer. If (I) shows geometric asymmetry, then (I) in the cis or trans form is used. (I) is used in combination with at least one vaccine.

Administration is parenteral or oral.

SPECIFIC COMPOUNDS

The use of 15 compounds (I) is specifically claimed e.g.

(1,1'-biphenyl)-4-acetic acid-, 2-fluoro-alpha-methyl-,2-methoxy-4-((1E)-3-(4-(nitrooxy)butoxy)-3-oxo-1-p openyl)phenyl ester (Ia).

TITLE-TERMS: DERIVATIVE TREAT DISEASE

DERWENT-CLASS: B05

CPI-CODES: B06-D01; B10-A03; B14-J01A4;

CHEMICAL-CODES: Chemical Indexing M2 *01* Fragmentation Code G010 G015 G019 G100 H5 H541 H6 H601 H641 H7 H721 H8 J0 J012 J2 J241 J271 K0 K7 K710 M1 M111 M210 M211 M272 M281 M312 M314 M321 M322 M331 M332 M340 M342 M372 M383 M391 M392 M414 M431 M510 M520 M533 M540 M782 P446 Specific Compounds RA2T9J Registry Numbers 336322

Chemical Indexing M2 *02*

Fragmentation Code G013 G015 G100 H5 H541 H7 H721 H8 J0 J012 J2 J241 J271 K0 K7 K710 M210 M211 M214 M232 M240 M272 M281 M312 M314 M321 M322 M331 M332 M340 M342 M372 M383 M391 M392 M414 M431 M510 M520 M532 M540 M782 P446 Specific Compounds RA2T9H Registry Numbers 336320

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Chemical Indexing M2 *05*
Fragmentation Code G010 G015 G100 H6 H601 H641 J0 J012 J2 J272 J290 J3 J371 J9 K0 K7 K710 M1 M111 M210 M211 M262 M281 M312 M314 M321 M322 M331 M332 M340 M342 M343 M349 M372 M381 M383 M391 M414 M431 M510 M520 M532 M540 M782 P446 Specific Compounds RA2T9F Registry Numbers

336318

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Chemical Indexing M2 *07*
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Chemical Indexing M2 *08*
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K710 M1 M121 M143 M210 M211 M262 M281 M311 M312 M314 M321 M332 M342 M343 M349 M372 M381 M383 M391 M414 M431 M510 M520 M532 M540 M782 P446 Specific Compounds RA99QQ Registry Numbers 650135

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Chemical Indexing M2 *15*
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M520 M533 M540 M782 P446 Specific Compounds RA2T9J Registry Numbers 336322

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M211 M262 M281 M312 M314 M321 M322 M331 M332 M340 M342 M343 M349 M372 M381 M383 M391 M414 M431 M510 M520 M532 M540 M782 P446 Specific Compounds RA2T9F Registry Numbers 336318

Chemical Indexing M2 *21* Fragmentation Code D014 D022 D601 G013 G100 H2 H211 H5 H541 H6 H602 H641 H8 J0 J013 J2 J272 J290 J3 J331 J371 J9 K0 K7 K710 M210 M211 M240 M262 M272 M281 M311 M312 M314 M321 M332 M342 M343 M349 M372 M381 M383 M391 M412 M431 M511 M520 M531 M540 M782 P446 Specific Compounds RA2T9E Registry Numbers 336317

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Fragmentation Code G015 G100 H4 H401 H441 H5 H541 H7 H721 H8 J0 J011 J2 J271 K0 K7 K710 M210 M211 M272 M281 M312 M314 M321 M332 M342 M372 M383 M391 M414 M431 M510 M520 M531 M540 M782 P446 Specific Compounds RA3O07 Registry Numbers 377170

Chemical Indexing M2 *26*
Fragmentation Code G012 G015 G100 H4 H401 H441 H5 H541 H7 H721 H8 J0 J011 J2 J241 K0 K7 K710 M210 M211 M272 M281 M311 M312 M321 M332 M342 M372 M373 M391 M414 M431 M510 M520 M532 M540 M782 P446 Specific Compounds RA99QR Registry Numbers 650136

Chemical Indexing M2 *27*
Fragmentation Code C017 C100 C800 C801 C803 C804 C805 C806 C807 F012 F016 F431 G015 G100 H4 H401 H441 H5 H541 H7 H721 H8 J0 J011 J2 J271 K0 K7 K710 M210 M211 M272 M281

M311 M312 M321 M322 M332 M342 M372 M373 M391 M392 M411 M431 M510 M521 M531 M540 M640 M782 P446 Specific Compounds RA99QS Registry Numbers 650137

Chemical Indexing M2 *28* Fragmentation Code G010 G015 G100 H6 H601 H641 J0 J011 J2 J271 J5 J581 K0 K7 K710 L5 L560 M1 M111 M280 M314 M321 M332 M342 M383 M391 M414 M431 M510 M520 M532 M540 M782 P446 Specific Compounds RA99QT Registry Numbers 650138

Chemical Indexing M2 *29* Fragmentation Code G015 G100 H4 H401 H441 H5 H541 H7 H721 H8 J0 J012 J2 J272 J290 J3 J371 J9 K0 K7 K710 M210 M211 M262 M272 M281 M312 M314 M321 M322 M332 M342 M343 M349 M372 M381 M383 M391 M414 M431 M510 M520 M531 M540 M782 P446 Specific Compounds RA99QU Registry Numbers 650139

Chemical Indexing M2 *30* Fragmentation Code G015 G019 G100 H4 H401 H441 H5 H542 H7 H722 H8 J0 J012 J2 J241 J271 K0 K7 K710 M210 M211 M272 M282 M312 M314 M321 M322 M332 M342 M372 M383 M391 M392 M414 M431 M510 M520 M532 M540 M782 P446 Specific Compounds RA99QV Registry Numbers 650140

Chemical Indexing M2 *31* Fragmentation Code C116 D010 D020

D040 F010 F011 F012 F013 F014 F015
F016 F017 F019 F020 F021 F029 F123
F433 F653 G001 G002 G003 G010 G011
G012 G013 G014 G015 G016 G017 G019
G020 G021 G022 G029 G030 G033 G034
G035 G036 G037 G038 G039 G040 G050
G100 G111 G112 G113 G221 G553 G563
H1 H102 H103 H121 H122 H141 H181
H201 H211 H401 H421 H461 H521 H561
H581 H598 H600 H602 H608 H609 H621
H622 H641 H642 H643 H661 H662 H685
H689 H721 J011 J012 J271 J290 J331
J371 J5 J561 J581 J582 J583 K0
K224 K353 K433 K640 K7 K710 K799
K850 K899 K930 L560 L640 L650 L660
M113 M116 M123 M125 M126 M129 M131
M132 M135 M139 M143 M210 M211 M212
M213 M214 M215 M216 M220 M221 M222
M223 M224 M225 M226 M231 M232 M233
M240 M272 M273 M281 M282 M283 M311
M312 M313 M314 M315 M316 M321 M322
M323 M331 M332 M333 M340 M342 M343
M344 M349 M353 M372 M373 M381 M382
M383 M391 M392 M393 M412 M413 M414
M415 M431 M510 M511 M521 M522 M523
M530 M531 M532 M533 M540 M541 M542
M543 M782 P446 Markush Compounds
008343201

Chemical Indexing M2 *32*
Fragmentation Code C116 D010 D020
D040 F010 F011 F012 F013 F014 F015
F016 F017 F019 F020 F021 F029 F123
F433 F653 G001 G002 G003 G010 G011
G012 G013 G014 G015 G016 G017 G019
G020 G021 G022 G029 G030 G033 G034
G035 G036 G037 G038 G039 G040 G050
G100 G111 G112 G113 G221 G553 G563

H1 H102 H103 H121 H122 H141 H181
H201 H211 H401 H421 H461 H521 H561
H581 H598 H600 H602 H608 H609 H621
H622 H641 H642 H643 H661 H662 H685
H689 H721 J011 J012 J271 J290 J331
J371 J5 J561 J581 J582 J583 K0
K224 K353 K433 K640 K7 K710 K799
K850 K899 K930 L560 L640 L650 L660
M113 M116 M123 M125 M126 M129 M131
M132 M135 M139 M143 M210 M211 M212
M213 M214 M215 M216 M220 M221 M222
M223 M224 M225 M226 M231 M232 M233
M240 M272 M273 M281 M282 M283 M311
M312 M313 M314 M315 M316 M321 M322
M323 M331 M332 M333 M340 M342 M343
M344 M349 M353 M372 M373 M381 M382
M383 M391 M392 M393 M412 M413 M414
M415 M431 M510 M511 M521 M522 M523
M530 M531 M532 M533 M540 M541 M542
M543 M782 P446 Markush Compounds
008343201

SECONDARY-ACC-NO:

CPI Secondary Accession Numbers: 2003-028712